Remarks

The November 7, 2003 Advisory Action has been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

In the Advisory Action, the Examiner has indicated that the amendment presented in the response to the Official Action filed on October 24, 2003 will not be entered into the case because the amendment allegedly raises the issue of new matter. Additionally, the Examiner has noted that the exhibit of Perlstein et al. will not be entered into the application because the reference is allegedly not solely directed to the issues that were newly raised by the Examiner in the final rejection.

The Examiner has maintained the rejection of claims 34 and 37 for allegedly failing the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner has also maintained the rejection of claims 1, 3-5, 38, and 39 under 35 U.S.C. §112, first paragraph for allegedly failing the enablement requirement.

The Examiner has also objected to the application for not cancelling claims withdrawn from consideration. The cancellation of claims 2, 6, 10, 11, 13, 17, 19, 20, 22-25, and 29-31 overcomes this objection. Applicants reserve the right to file one or more continuing applications under 35 U.S.C. §120 on the subject matter of claims cancelled or withheld from consideration.

The foregoing rejection constitutes all of the grounds set forth in the November 7, 2003 Advisory Action for refusing allowance of the present application.

CLAIM 34 AND CLAIM 37, AS PRESENTLY AMENDED, FULLY COMPLY WITH THE REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has maintained that the originally filed specification fails to support the recitation of "vascular

smooth muscle cell" in claim 34. Specifically, the Examiner contends that the utilization of rat A10 cells in Examples 1-3 is insufficient to claim the entire genus of vascular smooth muscle cells without general reference in the specification to applying the method of the claimed invention to vascular smooth muscle cells.

Applicants respectfully disagree with the Examiner. Specifically, at page 24, lines 1 through 4, tenascin C is described as altering vascular smooth muscle cell morphology and proliferation response of the same. Additionally, as noted in the October 24, 2003 response to the previous Official Action and in the present examples, tenascin C was shown to improve the transfection efficiency of vascular smooth muscle cells (rat A10 cells; see, e.g., Example 2). Combining the disclosure at page 24 and the requirement in claim 27 that tenascin C cause "the morphology of a cell to change" which enhances efficiency of the delivery of a nucleic acid into the cells, Applicants contend use of vascular smooth muscle cells was adequately described in the application as filed and that Applicants possessed the invention claimed in claim 34 at the time of filing.

In light of the foregoing remarks, Applicants contend the rejection of claim 34 under 35 U.S.C. §112, first paragraph is untenable and should be withdrawn. However, if the Examiner remains unconvinced, Applicants are amenable to cancellation of the claim by Examiner amendment in order to expedite allowance of the present application.

The Examiner has also maintained the written description rejection of claim 37 for the recitation of "a carrier that permits controlled release of" tenascin C. The Examiner did not enter the proposed amendment to claim 37 set forth in the October 24, 2003 response to the previous Official Action because the proposed claim amendment allegedly introduced new matter. Specifically, the Examiner claims the specification fails to provide recitation for carriers that are not

polymeric.

Again, in an effort to place the instant application in condition for allowance, Applicants have amended claim 37 to recite a "polymeric carrier being selected from the group consisting of controlled release film, nanoparticle, and microparticle carrier." Support for this amendment can be found at page 16, lines 12-13 of the specification.

Inasmuch as the subject matter of claim 34 and presently amended claim 37 is fully described in the present specification, the 35 U.S.C. §112, first paragraph rejection of these claims is improper and should be withdrawn.

CLAIM 1, AS AMENDED, AND CLAIMS 3-5 FULLY COMPLY WITH THE ENABLEMENT REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has maintained the rejection of claims 1, 3-5, 38, and 39 as allegedly failing to comply with the enablement requirement under 35 U.S.C. §112, first paragraph. Particularly, it is the Examiner's position that the specification, while being enabling for enhancing transfection of cultured cells with plasmids contained in cationic liposomes in the presence of tenascin C, fails to provide enablement for *in vivo* methods and for vectors other than plasmid vectors. Applicants respectfully disagree.

Claims 38 and 39 were rejected by the Examiner in the August 22, 2003 Official Action because the compositions of these claims are taught in the specification to be directed to *in vivo* uses. Additionally, claims 1 and 3-5 were rejected for encompassing *in vivo* methods. It is unfortunate that the Examiner chose not to consider the exhibit of Perlstein et al. because the reference demonstrates the ability of denatured collagen to enhance cell transfection *in vivo* and therefore provides compelling evidence that the claimed method functions *in vivo*. Additionally, Applicants maintain that the instant specification, as originally filed, is adequately enabled for

a skilled artisan to practice the *in vivo* methods of the claimed invention. However, in an effort to place the instant application in condition for allowance, Applicants have cancelled claims 38 and 39 and amended claim 1, upon which claims 3-5 are dependent, to recite an *in vitro* method of enhancing the efficiency of nucleic acid delivery to cells.

Claims 1 and 3-5 are also rejected under 35 U.S.C. §112, first paragraph because the specification, while enabled for delivery of a plasmid vector in cationic liposomes, allegedly does not provide enablement for the delivery of other types of vectors. The Examiner contends that a skilled artisan would not be able to predict that other types of vectors would be enhanced in transfection efficiency, as was the case with plasmid vectors in cationic liposomes.

Applicants respectfully disagree with the Examiner. The test for enablement is the balancing of several specifically prescribed factors listed in MPEP § 2164.01(a). These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. (Citation omitted.)

Applicants respectfully submit that, with regard to the art of delivering a nucleic acid to a cell by a vector, the

state of the prior art is very high and very predictable and an artisan in the field is highly skilled. Applicants have also provided working examples in which the plasmid vector in cationic liposomes can be readily replaced by other vectors provided in the specification, such as viral vectors and "naked" nucleic acids. Moreover, adequate direction for performing the claimed method with other vectors are provided, in part, by reference to Ausubel et al. and Sambrook et al. (page 16, line 27 through page 17, line 1), which are incorporated into the specification by said reference (see page 30, lines 19 and 20). Indeed, chapter 9 of Ausubel et al., for example, provides explicit instructions for the delivery of nucleic acids to a cell via vectors other than plasmid vectors in cationic liposomes. Inasmuch as functioning examples are provided in which other vectors may be tested and methods for utilizing these other vectors are clearly provided, Applicants also contend the quantity of experimentation necessary to use the method as claimed would be minimal. Thus, when all of the factors set forth in the enablement test are considered, Applicants contend the claimed invention is fully enabled by the specification.

In light of all the foregoing, the rejection of claims 1, 3-5, 38, and 39 under 35 U.S.C. §112, first paragraph is clearly improper and Applicants respectfully request its withdrawal. However, if the Examiner is not persuaded by the foregoing argument regarding the enablement of methods for delivery of a nucleic acid which encompasses naked DNA and viral vectors, Applicants are prepared to amend claim 1 to recite the delivery of a nucleic acid "in a plasmid vector contained in cationic liposomes."

Conclusion

It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in

nature. The amendments are believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case

In view of the amendments and remarks presented herewith, it is respectfully urged that the rejections set forth in the November 7, 2003 Advisory Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any issues outstanding may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By _____
Kathleen D. Rigaut, Ph.D., J.D.
PTO Registration No. 43,047

Telephone: (215) 563-4100